search notes 10/030,294

***603273**

GeneTests, Links

TUMOR PROTEIN p73-LIKE; TP73L

Alternative titles; symbols

TUMOR PROTEIN p63; TP63
p53-RELATED PROTEIN p63; p63
KET

Gene map locus 3q27

TEXT

Yang et al. (1998) described the cloning of tumor protein p63, which shows strong homology to the tumor suppressor p53 (191170) and the p53-related protein p73 (601990). p63 was detected in a variety of human and mouse tissues, including proliferating basal cells of epithelial layers in the epidermis, cervix, urothelium, and prostate. Unlike p53, the p63 gene encodes multiple isotypes with remarkably divergent abilities to transactivate p53 reporter genes and induce apoptosis. The predominant p63 isoforms in many epithelial tissues lack an acidic N terminus corresponding to the transactivation domain of p53. The full-length p63 has 15 exons and encodes a protein of 448 amino acids. Isoforms of p63 are due to alternative promoters in exons 1 or 3 and alternative splicing of exons at the 3-prime end. These truncated p63 variants can act as dominant-negative agents toward transactivation by p53 and p63. Yang et al. (1998) suggested the possibility of physiologic interactions among members of the p53 family.

Augustin et al. (1998) also cloned a cDNA, which they termed KET, that is related to the tumor suppressor p53. They stated that the 4,846-bp KET cDNA encodes a protein of 680 amino acids that shares 98% identity with the rat homolog. The remarkable degree of conservation lent support to the notion that KET proteins have important basic functions in development and differentiation.

Hibi et al. (2000) stated that p53 homologs known variously as p40, p51, p63, and p73L (Trink et al., 1998, Yang et al., 1998, Osada et al., 1998, Senoo et al., 1998) are isoforms of the same gene, which Hibi et al. (2000) referred to as AIS for 'amplified in squamous cell carcinoma.' The main difference between the various transcripts is the presence or absence of the N-terminal transcriptional activation domain; p40, delta-Np63, and p73L lack this domain. Though no evidence of a tumor suppressor function was found, Hibi et al. (2000) observed overexpression of this gene in head and neck cancer cell lines and

primary lung cancers associated with a low increase of its copy number. Amplification of the AIS locus was accompanied by RNA and protein overexpression of a variant p68(AIS) lacking the terminal transactivation domain. Protein overexpression in primary lung tumors was limited to squamous cell carcinoma and tumors known to harbor a high frequency of p53 mutations. Overexpression of p40(AIS) in Rat 1a cells led to an increase in soft agar growth and tumor size in mice. Results were interpreted as indicating that AIS transcripts lacking the N-terminal transcriptional activation domain play an oncogenic rather than a suppressive role in certain cancers.

By fluorescence in situ hybridization, Yang et al. (1998) localized the human TP63 gene to 3q27-q29. Using linkage analysis, they mapped the mouse gene to chromosome 16 in a region known to be syntenic with human 3q27-q29. By radiation hybrid analysis, Augustin et al. (1998) mapped the KET gene to human 3q27. KET is located between the somatostatin gene (SST; 182450) proximally and the apolipoprotein D gene (APOD; 107740) distally. By means of an interspecific backcross panel, Augustin et al. (1998) mapped the murine homolog, Ket, to chromosome 16 in a region that is deleted in early stages of tumorigenesis of mouse islet cell carcinomas and contains the Loh2 gene, a putative suppressor of angiogenesis. Augustin et al. (1998) inferred from mapping data that KET may act as a tumor suppressor and should be considered a candidate for Loh2.

Celli et al. (1999) mapped EEC3 (604292), an autosomal dominant disorder characterized by ectrodactyly, ectodermal dysplasia, and facial clefts, to a region of 3q27 where an EEC-like disorder, limb-mammary syndrome (LMS; 603543), had been mapped. Analysis of the p63 gene, which is located in the critical LMS/EEC3 interval, revealed heterozygous mutations in 9 unrelated EEC3 families. Eight mutations resulted in amino acid substitutions that were predicted to abolish the DNA binding capacity of p63; the ninth was a frameshift mutation. Six of the 9 mutations were C-to-T transversions at CpG dinucleotides. Transactivation studies with these mutant p63 isotypes provided a molecular explanation for the dominant character of p63 mutations in EEC3.

To assess the potential of p63 as a candidate gene for split-hand/foot malformation (SHFM4; 605289), Ianakiev et al. (2000) analyzed the p63 gene in 2 multigenerational families with SHFM in which segregation analysis had excluded linkage to all previously identified autosomal regions. Two missense mutations, 724A-G in exon 5, which predicted a lys194-to-glu substitution (603273.0005), and 982T-C in exon 7, which predicted an arg280-to-cys substitution (603273.0006). Ianakiev et al. (2000) also identified mutations in the TP63 gene in families with EEC3; see 603273.0007 and 603273.0008. All 4 TP63 mutations identified by Ianakiev et al. (2000) were found in exons that fall within the DNA-binding domain of p63. The 2 amino acids mutated in the families with SHFM appeared to be involved primarily in maintenance of the overall structure of the domain, in contrast to the p63 mutations responsible for EEC syndrome, which reside in amino acid residues that directly interact with DNA.

Hay-Wells syndrome, also known as ankyloblepharon-ectodermal dysplasia-clefting (AEC) syndrome (106260), is a rare autosomal dominant disorder characterized by congenital ectodermal dysplasia, including alopecia, scalp infections, dystrophic nails, hypodontia, ankyloblepharon, and cleft lip and/or cleft palate. This constellation of clinical signs is unique, but some overlap can be recognized with other ectodermal dysplasia

syndromes, including ectrodactyly-ectodermal dysplasia-cleft lip/palate (EEC; 604292), limb-mammary syndrome (LMS; 603543), acro-dermato-ungual-lacrimal-tooth syndrome (ADULT; 103285), and recessive cleft lip/palate-ectodermal dysplasia (CLPED1; 225000). McGrath et al. (2001) analyzed the p63 gene in AEC syndrome patients and identified missense mutations in 8 families. All mutations gave rise to amino acid substitutions in the sterile alpha motif (SAM) domain, and were predicted to affect protein-protein interactions. In contrast, the vast majority of the mutations found in EEC syndrome are amino acid substitutions in the DNA-binding domain. The authors suggested that a distinct genotype-phenotype correlation can be recognized for EEC and AEC syndromes.

Amiel et al. (2001) reported a missense mutation (603273.0011) in the TP63 gene in an isolated case of acro-dermato-ungual-lacrimal-tooth (ADULT) syndrome (103285), which maps to chromosome 3q27. The mutation was inherited from the healthy father, in whom freckling of the back and shoulders was the only feature of ADULT syndrome. Amiel et al. (2001) considered incomplete penetrance as the most likely explanation.

Flores et al. (2002) explored the role of p63 and p73 in DNA damage-induced apoptosis. Mouse embryo fibroblasts deficient for 1 or a combination of these p53 family members were sensitized to undergo apoptosis through the expression of the adenovirus E1A oncogene. While using the E1A system facilitated the performance of biochemical analyses, the authors also examined the functions of p63 and p73 using an in vivo system in which apoptosis had been shown to be dependent on p53. Using both systems, Flores et al. (2002) demonstrated that the combined loss of p63 and p73 results in the failure of cells containing functional p53 to undergo apoptosis in response to DNA damage.

Van Bokhoven and Brunner (2002) reviewed the spectrum of p63 mutations underlying 5 human malformation syndromes. The localization and functional effects of the mutations established a striking genotype-phenotype correlation. Functional analysis of these mutations provided valuable new insights into p63 protein structure and function and provided a basis for further dissection of molecular and cellular pathways involving p63. Clustering of mutations establish a clear genotype-phenotype correlation: in the DNA binding domain (DBD) for EEC syndrome and in the SAM domain for AEC syndrome. Limb-mammary syndrome (LMS; 603543) differs from EEC syndrome in at least 3 respects: (1) mammary gland and nipple hypoplasia are consistent features of LMS but are only occasionally seen in EEC syndrome; (2) patients with LMS do not have the hair and skin defects that are seen in EEC syndrome; (3) whereas patients with LMS have cleft palate, those with EEC syndrome have cleft lip/palate but never have cleft palate only. Phenotypically, LMS is most similar to ADULT syndrome. Two isolated patients with an LMS phenotype had, in exons 13 and 14, frameshift mutations that resulted in truncation of the p63-alpha protein. Therefore, the abundant p63 product in epithelial cells would be missing the transactivation inhibitory domain (TID).

Brunner et al. (2002) reviewed p63 mutations causing developmental syndromes. They stated that the pattern of heterozygous mutations is distinct for each syndrome, and that consistent with this syndrome-specific mutation pattern, the functional consequences of mutations on the p63 proteins also vary, invoking dominant-negative and gain-of-function mechanisms rather than a simple loss of function.

Benard et al. (2003) suggested that the 2 homologs of TP53, TP73 and TP63, must not have a typical tumor suppressor gene role in human cancers, given the lack of demonstrated mutations in either of these 2 genes. Nevertheless, TP73 and TP63 seem strongly involved in malignancy acquisition and maintenance.

ANIMAL MODEL

Yang et al. (1999) generated mice deficient in p63 by targeted disruption. p63 -/- mice have major defects in their limb, craniofacial, and epithelial development. p63 is expressed in the ectodermal surfaces of the limb buds, branchial arches, and epidermal appendages, which are all sites of reciprocal signaling that direct morphogenetic patterning of the underlying mesoderm. The limb truncations are due to a failure to maintain the apical ectodermal ridge, which is essential for limb development. The embryonic epidermis of p63 -/- mice undergoes an unusual process of nonregenerative differentiation, culminating in a striking absence of all squamous epithelia and their derivatives, including mammary, lacrimal, and salivary glands. Yang et al. (1999) concluded that p63 is critical for maintaining the progenitor-cell populations that are necessary to sustain epithelial development and morphogenesis.

Mills et al. (1999) independently generated mice deficient in p63. The p63-deficient mice were born alive but had striking developmental defects. Their limbs were absent or truncated, defects that were caused by a failure of the apical ectodermal ridge to differentiate. The skin of p63-deficient mice did not progress past an early developmental stage: it lacked stratification and did not express differentiation markers. Structures dependent upon epidermal-mesenchymal interactions during embryonic development, such as hair follicles, teeth, and mammary glands, were absent in p63-deficient mice.

ALLELIC VARIANTS
(selected examples)

.0001 ECTRODACTYLY, ECTODERMAL DYSPLASIA, AND CLEFT LIP/PALATE SYNDROME 3 [TP73L, ARG204TRP]

In 3 unrelated patients with EEC3 (604292), Celli et al. (1999) identified a heterozygous arg204-to-trp mutation in the DNA binding domain of TP63. The mutation segregated with the disease in 2 families and was not found in normal controls. In the third family, the mutation occurred de novo.

.0002 ECTRODACTYLY, ECTODERMAL DYSPLASIA, AND CLEFT LIP/PALATE SYNDROME 3 [TP73L, ARG204GLN]

In a patient with EEC3 (604292), Celli et al. (1999) identified a heterozygous arg204-to-gln mutation in the core element II of the DNA binding domain of TP63. The mutation segregated with the disease and was not found in normal controls.

.0003 ECTRODACTYLY, ECTODERMAL DYSPLASIA, AND CLEFT LIP/PALATE SYNDROME 3 [TP73L, CYS306ARG]

In a patient with EEC3 (604292), Celli et al. (1999) identified a heterozygous cys306-to-arg mutation in the core element IV of the DNA binding domain of TP63. The mutation was de novo and was not found in normal controls. Transactivation assays using cell lysates containing the cys306-to-arg mutation showed a total lack of transactivation activity.

.0004 ECTRODACTYLY, ECTODERMAL DYSPLASIA, AND CLEFT LIP/PALATE SYNDROME 3 [TP73L, 1-BP INS, 1572A]

In a patient with EEC3 (604292), Celli et al. (1999) identified a 1-bp insertion (A) at nucleotide 1572 in exon 13 of the TP63 gene, resulting in a frameshift at codon 525 (tyr) and a premature stop codon in the same exon. The mutation was de novo.

.0005 SPLIT-HAND/FOOT MALFORMATION 4 [TP73L, LYS194GLU]

In a family with SHFM4 (605289) from South Africa, previously reported by Spranger and Schapera (1988), Ianakiev et al. (2000) identified a 724A-G transition in exon 5 of the p63 gene, predicted to cause a lys194-to-glu (K194E) amino acid substitution. This family, designated R, was of mixed ancestry from Cape Province. The spectrum of clinical manifestations was broad, ranging from the presence of a split hand in 1 individual to bilateral monodactyly and unilateral aplasia of the right lower extremity with a split left foot in another individual. No family members had any significant abnormalities other than those of the extremities.

.0006 SPLIT-HAND/FOOT MALFORMATION 4 [TP73L, ARG280CYS]

In a family of mixed ancestry from Cape Province, South Africa, with SHFM4 (605289), Ianakiev et al. (2000) identified a 982T-C transition in exon 7 of the TP63 gene, predicted to cause an arg280-to-cys (R280C) amino acid substitution. The phenotype in this family, designated A, ranged from severe 'lobster claw' malformations of the feet in 1 individual, to minor 3/4 syndactyly of the left foot appearing as the only manifestation in another individual. The daughter of the latter individual had distal duplications of her thumbs bilaterally with absence of the second and third phalanges of the right hand and an absent second phalanx with 3/4 syndactyly of the left hand. No members of the family had significant abnormality of the face, palate, skin, teeth, hair, or nails. No abnormalities of the mammary glands or nipples were noted.

.0007 ECTRODACTYLY, ECTODERMAL DYSPLASIA, AND CLEFT LIP/PALATE SYNDROME 3 [TP73L, ARG279HIS]

In a study of 4 European families with EEC3 (604292), Ianakiev et al. (2000) identified heterozygosity for 2 missense mutations in the TP63 gene: a G-to-A transition at nucleotide 980 in exon 7 that predicts an arg279-to-his (R279H) substitution, and a G-to-A transition at nucleotide 1065 in exon 8 that predicts an arg304-to-gln (R304Q) substitution (603273.0008).

.0008 ECTRODACTYLY, ECTODERMAL DYSPLASIA, AND CLEFT LIP/PALATE SYNDROME 3 [TP73L, ARG304GLN]

See 603273.0007 and Ianakiev et al. (2000).

.0009 ANKYLOBLEPHARON-ECTODERMAL DEFECTS-CLEFT LIP/PALATE [TP73L, LEU514PHE]

In a 6-year-old patient with Hay-Wells syndrome (106260) who lacked any limb defects, McGrath et al. (2001) identified an A-to-T transversion at nucleotide 1542 of the TP63 gene, resulting in a leu518-to-phe substitution in the sterile alpha motif (SAM) domain. Molecular modeling suggested that the substitution would alter protein-protein interactions. According the sequence reported by Yang et al. (1998), this mutation is designated leu514 to phe.

.0010 ANKYLOBLEPHARON-ECTODERMAL DEFECTS-CLEFT LIP/PALATE [TP73L, CYS522GLY]

In a 10-month-old infant with typical features of Hay-Wells syndrome (106260), McGrath et al. (2001) identified a T-to-G transversion at nucleotide 1564 of the TP63 gene, resulting in a cys526-to-gly substitution in the sterile alpha motif (SAM) domain. Molecular modeling suggested that the substitution would alter protein-protein interactions. According the sequence reported by Yang et al. (1998), this mutation is designated cys522 to gly.

.0011 ADULT SYNDROME [TP73L, ASN6HIS]

In a 10.5-year-old patient with features of acro-dermato-ungual-lacrimal-tooth (ADULT) syndrome (103285), Amiel et al. (2001) described a heterozygous A-to-C transversion at position 16 in exon 3-prime of the TP63 gene, resulting in an asn6-to-his (N6H) substitution between the transactivation and DNA binding domains. The mutation affected exon 3-prime present only in the isotypes lacking the transactivation domain of the protein. The mutation was inherited from the healthy father, in whom freckling of the back and shoulders was the only feature of ADULT syndrome, and was absent from a panel of 250 control chromosomes. Amiel et al. (2001) considered incomplete penetrance as the most likely explanation.

.0012 LIMB-MAMMARY SYNDROME [TP73L, 2-BP DEL, 1576TT]

In each of 2 isolated cases of limb-mammary syndrome (603543), van Bokhoven et al. (2001) found frameshift mutations in exons 13 and 14 that resulted in truncation of the p63-alpha protein. Therefore, the abundant p63 product in epithelial cells would be missing from the transactivation inhibitory domain (TID). One was deletion of 2 nucleotides in exon 13 (1576delTT); the other was deletion of 2 nucleotides in exon 14 (1743delAA) (603273.0013). The numbering of the mutations is according to the sequence reported by Yang et al. (1998).

.0013 LIMB-MAMMARY SYNDROME [TP73L, 2-BP DEL, 1743AA]

See 603273.0012 and van Bokhoven and Brunner (2002).

.0014 ADULT SYNDROME [TP73L, ARG298GLN]

Duijf et al. (2002) reported a 2-generation family with acro-dermato-ungual-lacrimal-tooth (ADULT) syndrome (103285) whose affected individuals were heterozygous for an arg298-to-gln (R298Q) mutation. The mutation is located in the DNA binding domain of p63; however, unlike mutations in EEC syndrome, the R298Q mutation does not impair DNA binding. Rather, the mutation confers novel transcription activation capacity on the delta-N-p63-gamma isoform, which normally does not possess such activity. The authors concluded that p63 contains a second transactivation domain which is normally repressed and can become activated by mutations in the DNA binding domain of p63.

.0015 ECTRODACTYLY, ECTODERMAL DYSPLASIA, AND CLEFT LIP/PALATE SYNDROME 3 [TP73L, ASP312GLY]

In a Japanese girl who had EEC3 (604292) and developed diffuse large B-cell type non-Hodgkin lymphoma, Akahoshi et al. (2003) identified heterozygosity for a 1079A-G transition in exon 8 of the TP73L gene, resulting in a germline asp312-to-gly (D312G) mutation. They speculated that p63 may exert a biologic function as a tumor suppressor and suggested that malignant lymphoma should be considered an important complication of EEC3, inasmuch as 2 previous reports had also documented an association of EEC syndrome with malignant lymphoma (Gershoni-Baruch et al., 1997; Ogutcen-Toller et al., 2000).

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